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High-Sensitivity Cardiac Troponin on Presentation to Rule Out Myocardial Infarction: A Stepped-Wedge Cluster Randomized Controlled Trial

Running Title: *Anand, Lee, Chapman, et al.; The HiSTORIC Trial*

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Abstract

Background: High-sensitivity cardiac troponin assays enable myocardial infarction to be ruled out earlier, but the safety and efficacy of this approach is uncertain. We investigated whether an early-rule out pathway is safe and effective for patients with suspected acute coronary syndrome.

Methods: We performed a stepped-wedge cluster randomized controlled trial in the Emergency Departments of seven acute care hospitals in Scotland. Consecutive patients presenting with suspected acute coronary syndrome between December 2014 and December 2016 were included. Sites were randomized to implement an early rule-out pathway where myocardial infarction was excluded if high-sensitivity cardiac troponin I concentrations were <5 ng/L at presentation.

During a prior validation phase, myocardial infarction was ruled out where troponin concentrations were $<99^{\text{th}}$ centile at 6–12 hours after symptom onset. The co-primary outcome was length of stay (efficacy), and myocardial infarction or cardiac death after discharge at 30 days (safety). Patients were followed for 1 year to evaluate safety and other secondary outcomes.

Results: We enrolled 31,492 patients (59 ± 17 years, 45% women) with troponin concentrations $<99^{\text{th}}$ centile at presentation. Length of stay was reduced from 10.1 ± 4.1 to 6.8 ± 3.9 hours (adjusted geometric mean ratio 0.78, 95% confidence interval [CI] 0.73 to 0.83, $P < 0.001$) following implementation, and the proportion of patients discharged increased from 50% to 71% (adjusted odds ratio [aOR] 1.59, 95% CI 1.45 to 1.75). Non-inferiority was not demonstrated for the 30-day safety outcome (upper limit of one-sided 95% CI for adjusted risk difference 0.70%, non-inferiority margin 0.50%, $P = 0.068$), but the observed differences favoured the early rule-out pathway (0.4% [57/14,700] *versus* 0.3% [56/16,792]). At 1 year, the safety outcome occurred in 2.7% (396/14,700) and 1.8% (307/16,792) of patients before and after implementation (aOR 1.02, 95% CI 0.74 to 1.40, $P = 0.894$), and there were no differences in hospital reattendance or all-cause mortality.

Conclusions: Implementation of an early rule-out pathway for myocardial infarction reduced length of stay and hospital admission. Whilst non-inferiority for the safety outcome was not demonstrated at 30 days, there was no increase in cardiac events at 1 year. Adoption of this pathway would have major benefits for patients and healthcare providers.

Clinical Trial Registration: URL: <https://www.clinicaltrials.gov> Unique Identifier: NCT03005158

Key Words: high-sensitivity cardiac troponin; early rule-out pathway; myocardial infarction; stepped-wedge cluster randomized controlled trial

Non-standard Abbreviations and Acronyms

HiSTORIC	High-Sensitivity cardiac Troponin On presentation to Rule out myocardial InfarCtion trial
High-STEACS	High-Sensitivity Troponin in the Evaluation of patients with suspected Acute Coronary Syndrome early rule-out pathway
LoDED	Limit of Detection and ECG Discharge trial
NHS	National Health Service
RAPID-TnT	Rapid assessment of possible acute coronary syndrome in the emergency department with high-sensitivity Troponin T trial

Clinical Perspective

What is new?

- Patients with suspected acute coronary syndrome frequently attend Emergency Departments, but the majority do not have myocardial infarction.
- Across 31,492 consecutive patients presenting to seven hospitals, implementation of an early rule-out pathway for patients with suspected acute coronary syndrome reduced length of stay by 3.3 hours and hospital admissions by 59%.
- Non-inferiority was not demonstrated, but observed differences in myocardial infarction or cardiac death at 30 days and 1 year favoured the early rule-out pathway over standard care.

What are the clinical implications?



- Existing early rule-out pathways for myocardial infarction are largely based on observational studies or small trials of selected patients.
- This trial provides evidence in consecutive patients with suspected acute coronary syndrome that the use of an early rule-out pathway is both safe and effective.
- Adoption of an early-rule out pathway for myocardial infarction would have major benefits for both patients and healthcare providers.

Introduction

There are over 20 million presentations with suspected acute coronary syndrome each year in the US alone,¹ accounting for up to a tenth of hospital visits and 40 percent of unscheduled admissions.² Given that most patients do not have myocardial infarction,³ the adoption of effective and safe pathways to rule out myocardial infarction in the Emergency Department and avoid hospital admission would have a major impact on patient care and healthcare provision.

Cardiac troponin testing is an integral component of the assessment of patients with suspected acute coronary syndrome, with guidelines recommending serial testing to rule in and rule out myocardial infarction.⁴ The development of high-sensitivity cardiac troponin assays with enhanced precision at very low concentrations permits quantification well below the 99th centile diagnostic threshold for myocardial infarction.⁵ This advance has led to innovative pathways to rule out myocardial infarction more rapidly, either at presentation or within 3 hours that have been incorporated into clinical practice guidelines.⁶⁻¹⁴ However, these studies were observational, and there are few examples where the pathway guided patient care.^{15,16} The majority were modest in size, or enrolled selected low-risk patients, and therefore the true efficacy and safety of introducing these pathways into clinical practice remains uncertain.

Our aim was to determine the efficacy and safety of implementing an accelerated pathway where high-sensitivity cardiac troponin testing is used to rule out myocardial infarction at presentation in consecutive patients with suspected acute coronary syndrome.

Methods

Trial Design and Oversight

High-Sensitivity cardiac Troponin On presentation to Rule out myocardial Infarction (HiSTORIC) is a stepped-wedge cluster randomized controlled trial enrolling consecutive patients with suspected acute coronary syndrome across seven acute hospitals in Scotland. In this trial, the hospital site was the unit of randomization and therefore individual patient consent was not sought. Cluster randomization was necessary to avoid the risk of clinical error due to simultaneous use of different diagnostic pathways. The trial was approved by the Scotland A Research Ethics Committee and the conduct of the trial was periodically reviewed by an independent trial steering committee. All data were collected from the patient record and national registries, deidentified and linked in a data repository (DataLoch, Edinburgh, UK) within secure NHS safe havens.¹⁷

Trial Population

Sites were eligible if they had the capacity to introduce the early rule-out pathway and returned data to the national registry. All patients were identified by the attending clinician using an electronic form integrated into the care pathway at the time troponin was requested. Patients were eligible for inclusion if they presented to the Emergency Department or Acute Medical Receiving Unit with suspected acute coronary syndrome and had a high-sensitivity cardiac troponin I concentration within the normal reference range (less than the sex-specific 99th centile upper reference limit) at presentation. Patients were excluded if they presented with an out-of-hospital cardiac arrest or ST-segment elevation myocardial infarction, had been admitted previously during the trial or were not resident in Scotland.

Randomization

The trial was conducted across three phases (**Figure 1a**). During all phases of the trial a high-sensitivity cardiac troponin I assay with sex-specific 99th centile thresholds was used to guide care and rule-in myocardial infarction according to the Universal Definition of Myocardial Infarction.⁴ During a validation phase of 6-9 months, troponin testing was performed at presentation and repeated 6-12 hours after the onset of symptoms if indicated (standard care). In accordance with guidelines at the time of enrolment,^{4,18} myocardial infarction was ruled out where high-sensitivity cardiac troponin concentrations were less than the 99th centile at presentation if symptom onset was >6 hours from presentation, or following serial testing 6-12 hours from symptom onset in those presenting earlier. Sites were paired based on the expected number of patients and randomized to implement the early rule-out pathway (intervention) in one of three steps during a 6-month randomization phase. Finally, all sites completed an implementation phase of 6-9 months calendar matched to the validation phase where care was guided by the early rule-out pathway.

Intervention

The *High-Sensitivity Troponin in the Evaluation of patients with suspected Acute Coronary Syndrome (High-STEACS)* early rule-out pathway (**Figure 1b**) has been described previously.^{19,20} Myocardial infarction is ruled out in patients with troponin concentrations <5 ng/L at presentation, unless they present within 2 hours of symptom onset where testing is repeated 3 hours from presentation. Patients with troponin concentrations ≥ 5 ng/L at presentation are retested 3 hours after presentation, and myocardial infarction is ruled out if concentrations are unchanged (delta <3 ng/L) and remain below the 99th centile. To support implementation, we provided educational material and presentations at each site, a webapp (www.highsteacs.com),

and formal training for clinical staff in the Emergency Department (*Supplemental Material*).

Throughout the trial, all sites used the Abbott ARCHITECT_{STAT} high-sensitive troponin I assay to guide clinical decisions. This assay has an inter-assay coefficient of variation of less than 10% at 4.7 ng/L,^{8,21} and a 99th centile of 16 ng/L in women and 34 ng/L in men.²²

Trial Outcomes

We used regional and national registries to follow-up the trial population.^{17,23-24} Sequential hypothesis testing evaluated two co-primary outcomes in an *a-priori* defined hierarchical order: the primary efficacy outcome followed by the primary safety outcome. The primary efficacy outcome was length of stay, defined as the length of time from presentation to the Emergency Department until discharge from hospital. The safety outcome was myocardial infarction (type 1, type 4b or type 4c) or cardiac death after discharge which was evaluated at 30 days (primary) and 1 year (secondary) following presentation. These events were adjudicated by a panel blind to the study phase. All subsequent presentations where any troponin concentration was >99th centile were reviewed and adjudicated as described previously (*Supplemental Material*).^{17,25-26}

The secondary efficacy outcome measure was the proportion of patients discharged from the Emergency Department. Other safety outcome measures included myocardial infarction, cardiac death, cardiovascular death, all-cause death, unplanned coronary revascularisation and reattendances for any reason after discharge at 1 year. Adherence was evaluated for three prespecified components of the early rule-out pathway (*Supplemental Material*).

Statistical Analysis

The primary efficacy outcome was analysed using a linear mixed-effects regression model, adjusting for hospital site (random effect), season, time of presentation since start of study, and an indicator variable for whether the early rule-out pathway had been implemented. The primary

safety outcome was analysed using a logistic mixed-effects regression model adjusting for the same covariates. For the primary efficacy analysis, length of stay was log-transformed prior to analysis and results expressed as a geometric mean ratio. If the analysis of the primary efficacy outcome was significant at the 5% level, then we planned to perform a non-inferiority analysis of the primary safety outcome reporting a risk difference (intervention–standard care) and one-sided 95% confidence interval. If the upper limit of the one-sided 95% confidence interval was below a 0.5% non-inferiority margin, then non-inferiority was established, and if it was below 0% then superiority was established. A sensitivity analysis compared outcomes during the calendar matched period in the validation and implementation phases using the same regression model as for the primary analysis, but without adjustment for time or season. A number of other sensitivity analyses were performed (*Supplemental Material*).



Patient and public involvement

A patient review panel was consulted throughout the trial programme and provided input on the educational advice provided to clinicians following introduction of the new pathway. Qualitative research capturing the views and experiences of patients treated within these pathways will follow in a separate publication. Patients were not involved in the conception or design of the trial.

Data Sharing

The HiSTORIC trial makes use of multiple routine electronic health care data sources that are linked, deidentified and held in the NHS national safe haven, which is accessible by approved individuals who have undertaken the necessary governance training. Summary data can be made available upon request to the corresponding author.

Results

Trial Sites and Population

Seven acute hospitals were eligible and all participated (*Table I in the Supplement*). Between December, 2014, and December, 2016, a total of 31,492 consecutive patients with suspected acute coronary syndrome (59 ± 17 years, 45% women) met the inclusion criteria (*Figure 2*).

There were 14,700 (47%) and 16,792 (53%) patients assessed before and after implementation of the early rule-out pathway, respectively. Clinical characteristics were similar before and after implementation (*Table I*) and across all three phases of the trial (*Table II in the Supplement*).

The trial concluded in December, 2017 with 1 year of follow up available in 31,428 (99.8%) patients.

Primary and Secondary Efficacy Outcomes

Length of stay was reduced from 10.1 ± 4.1 to 6.8 ± 3.9 hours (adjusted geometric mean ratio 0.78, 95% confidence interval [CI] 0.73 to 0.83, $P<0.001$) following implementation of the early rule-out pathway (*Table 2, Figure 3*). The proportion of patients discharged from the Emergency

Department without hospital admission increased from 50% to 71% (adjusted odds ratio 1.59, 95% CI 1.45 to 1.75). Adherence to all three prespecified components of the early rule-out pathway was observed in 11,600/16,792 (69%) of patients.

Primary and Secondary Safety Outcomes

Before and after implementation of the early rule-out pathway, the primary safety outcome of myocardial infarction or cardiac death following discharge at 30 days occurred in 57/14,700 (0.4%) and 56/16,792 (0.3%) patients respectively (*Table 2*) with an adjusted odds ratio of 1.97 (95% CI 0.95 to 4.08, $P=0.068$). Comparing the rate of the primary safety outcome after implementation to the rate before, the upper limit of our one-sided 95% confidence interval for



the adjusted risk difference was 0.70%, exceeding our prespecified non-inferiority margin of 0.50%. The event rate at 30 days was lower than anticipated, and our regression model and prespecified sensitivity analyses gave divergent results (**Table III in the Supplement**). However, there were 703 (2.2%) patients with myocardial infarction or cardiac death following discharge at 1 year (**Figure 4**). Before and after implementation, the secondary safety outcome measure occurred in 396/14,700 (2.7%) and 307/16,792 (1.8%) patients, respectively (adjusted odds ratio 1.02, 95% CI 0.74 to 1.40, $P=0.894$). This comprised 238 (1.6%) patients with myocardial infarction and 176 cardiac deaths (1.2%) during standard care, with 184 (1.1%) patients with myocardial infarction and 143 (0.9%) cardiac deaths after implementation of the early rule-out pathway. Furthermore, the rate of all other safety outcome measures at 1 year did not differ before and after implementation (**Table 2**). The findings were consistent in a *post hoc* analysis of the safety outcome which included type 2 myocardial infarction events (**Table IV and Figure I in the Supplement**).

Sensitivity Analysis in Calendar Matched Validation and Implementation Phases

In total 18,241 (58%) patients attended during the calendar-matched phases with 8,673 (48%) and 9,568 (52%) evaluated during the validation and implementation phase respectively (**Table III in the Supplement**). Length of stay was reduced from 10.6 ± 4.1 to 6.8 ± 4.0 hours (adjusted geometric mean ratio 0.65, 95% CI 0.62 to 0.68) before and after implementation of the early rule-out pathway. The primary safety outcome occurred in 43/8,673 (0.5%) and 23/9,568 (0.2%) patients at 30 days, with an adjusted odds ratio of 0.48 (95% CI 0.29 to 0.80, $P=0.005$). The upper limit of our one-sided 95% confidence interval for the adjusted risk difference was -0.13%, which was below our superiority margin of 0%. The secondary safety outcome occurred in

251/8,673 (2.9%) and 161/9,568 (1.7%) patients at 1 year (adjusted odds ratio 0.58, 95% CI 0.47 to 0.71, $P < 0.001$).

Discussion

We evaluated the efficacy and safety of implementing an early rule-out pathway in 31,492 consecutive patients presenting with suspected acute coronary syndrome to the Emergency Department or Acute Medical Receiving Unit. Introducing the pathway into clinical practice reduced length of stay by 3.3 hours and increased the odds of patients avoiding hospital admission by 59%. Non-inferiority was not formally demonstrated, but the observed differences in myocardial infarction or cardiac death following discharge favoured the early rule-out pathway.



There are several strengths of our pragmatic trial design. First, we embedded our screening tool into the patient record to ensure we prospectively enrolled consecutive patients whom the attending clinician suspected acute coronary syndrome. This minimized the risk of selection bias, ensuring we did not limit our findings to low-risk patients or those presenting within working hours. Second, as the intervention was implemented at the hospital level, we did not seek individual patient consent. This reduced the risk of a Hawthorne effect where effectiveness is exaggerated through direct observation of clinical care by researchers. Third, our trial population was larger than the combined number of patients enrolled in 30 previous observational studies.^{27,28} This ensured we had a greater number of events to evaluate safety. Finally, we combined hospital-level data with established registries to ensure follow up was complete in 99.8% of participants, and that our panel was able to adjudicate all safety outcome events.

The High-STEACS early rule-out pathway determines whether a patient with suspected acute coronary syndrome requires hospital admission or can be safely discharged. It is based on three principles. First, patients with very low troponin concentrations are at low-risk of cardiac events.⁶ We defined the optimal risk stratification threshold as the highest concentration that gave a negative predictive value of >99.5% for myocardial infarction or cardiac death at 30 days,^{8,27} to maximize the effectiveness of this approach whilst maintaining safety. Second, increasing concentrations above this risk stratification threshold on repeat testing may be important, even if they remain within the normal reference range, and these patients require admission to measure peak troponin concentration.¹⁹ We define this using a change in concentration of ≥ 3 ng/L, based on the lowest measurable change that exceeds biological and analytical variation.²⁹ Third, to ensure our pathway is consistent with international guidelines,⁴ we applied the sex-specific 99th centile as the threshold to identify patients who require hospital admission. Adherence was good across all seven acute hospitals which is testament to the simplicity of the pathway and should encourage adoption.

Whilst many pathways that incorporate separate risk stratification and diagnostic thresholds have been described,^{12,30-32} these suffer from the same limitation as the High-STEACS pathway; no patient was managed according to these pathways during their derivation or validation. Guideline recommendations have therefore been based largely on observational data, with little understanding of the impact of these pathways in clinical practice. Here we have evaluated the implementation of an early rule-out pathway in a prospective randomized controlled trial of consecutive patients. We report substantial reductions in length of stay and increases in the proportion of patients avoiding hospital admission. Were these gains to be realized across healthcare systems, the benefits for both patients and providers would be

substantial. In the US alone, more than 20 million patients with suspected acute coronary syndrome attend Emergency Departments each year.¹ A reduction in the length of stay of 3 hours could save more than \$3.6 billion per annum on bed occupancy alone.³³

Despite these important reductions in length of stay, during the implementation phase the median stay was 6.8 hours, which is longer than reported in other evaluations of the implementation of early rule-out pathways.^{15,16,34} This difference likely reflects our enrollment of all consecutive patients rather than selected patients who are less likely to have co-morbid conditions requiring hospital admission. We also acknowledge that reductions in length of stay may differ in other healthcare settings. Although the European Society of Cardiology (ESC) guidelines have recommended high-sensitivity cardiac troponin testing and a 0/3-hour pathway based on the 99th centile since 2011,³⁵ we did not adopt this as our standard of care, but instead followed the recommendations of our national guidelines.¹⁸ During the design phase of the trial, we prospectively validated the ESC 0/3 hour high-sensitivity cardiac troponin pathway and demonstrated that the diagnostic performance of serial testing at presentation and 3 hours compared to serial testing at presentation and 6-12 hours after symptom onset was poor with a sensitivity and negative predictive value for myocardial infarction of 89.3% and 97.9%, respectively.¹⁹ Our findings were consistent with those from an independent validation in Australia and New Zealand,³⁶ and as a consequence the 2020 ESC guidelines no longer prefer this approach.³⁷ It is essential that more prospective trials are conducted in which clinical decisions are guided by new diagnostic approaches if we are to ensure our clinical practice guidelines are based on the highest quality evidence.

Implementation of our early rule-out pathway did not increase the rate of subsequent myocardial infarction or cardiac death. However, our results were highly sensitive to the model

specification. Although non-inferiority was not concluded for the primary safety outcome at 30 days, in our prespecified sensitivity analysis restricted to calendar matched periods, the early rule-out pathway was superior to standard care at 30 days and 1 year. These divergent results may be due to the low event rate at 30 days and narrow randomization phase leading to overfitting of the primary analysis model, additional secular changes not accounted for in the sensitivity analysis, or a true exposure-time effect whereby outcomes improved as the intervention became more firmly embedded into practice. We acknowledge that although the number of patients enrolled in each cluster (hospital) was large, the number of clusters was small, which may have made the trial more vulnerable to the effect of confounding bias occurring within individual sites. However, our analyses suggested that including site as a random effect in the model had negligible influence on the overall result. The low event rate for the safety outcome at 30 days and narrow randomization phase made it more likely for chance imbalances to occur between those managed according to the standard care and early rule-out pathway (*Figure II in the Supplement*). This may have produced partial confounding of our estimate of the effect of the intervention as the primary analysis model incorporates both vertical comparisons across sites as well as before-and-after comparisons within sites. Importantly, we also prespecified a calendar matched before-and-after sensitivity analysis that did not include a vertical comparison; the results of which favored the early-rule out pathway.

Is it plausible that the introduction of an early rule-out pathway could reduce the risk of subsequent cardiac events? By using a threshold well below the 99th centile to risk stratify patients and by recognizing that small changes in troponin concentration within the reference range may be important, we may have improved the evaluation of risk compared to using a single higher threshold to rule in and rule out myocardial infarction. This is supported by recent

observational studies, which report that using the 99th centile to rule out myocardial infarction at presentation and at 3 hours, misses 1 in 10 patients with myocardial infarction who would have been identified on serial testing 6-12 hours following the onset of symptoms.^{19,36,38} Furthermore, our pathway encourages serial testing to safely rule out myocardial infarction in early presenters, which is now recognized by international guidelines.^{37,39}

Our findings add to those from two recently published randomized trials. The RAPID-TnT study compared a 1-hour and 3-hour rule-out pathway in 3,378 patients, finding a 1-hour strategy reduced length of stay by 60 minutes and increased discharge rates from 32% to 45%.¹⁶ The trial concluded non-inferiority for an endpoint of all-cause mortality or myocardial infarction within 30 days, although there was an increase in secondary safety outcome events in the 1-hour pathway arm. Due to a perceived lack of equipoise the monitoring committee recommended the trial stop recruitment with just two-thirds of the target population enrolled, and only one patient had a type 1 myocardial infarction following discharge in each arm. The Limit of Detection and ECG Discharge (LoDED) trial compared standard guideline care with a rule-out pathway using the limit of detection of cardiac troponin in 632 patients.⁴⁰ The use of a single test approach did not increase the proportion of patients discharged from hospital within four hours of presentation. This surprising finding may have been due to the small sample size and insufficient power or the enrollment of selected lower risk patients with a normal electrocardiogram. It appears that the treating clinician determined the probability of myocardial infarction to be sufficiently low that admission to hospital was not required in both arms of the trial. However, consistent with our observations, the LoDED investigators report that a single test approach was acceptable to patients and clinicians and that pathway adherence was excellent.

We acknowledge several potential study limitations. First, whilst the early rule-out pathway was implemented across three steps in the randomization phase, we had to accept flexibility in the date of implementation (*Supplemental Material*). This limited our ability to interpret a planned sensitivity analysis within the randomization phase, when there were sites using both the standard care and early rule-out pathway. Second, we enrolled fewer than the 38,994 patients anticipated in our sample size calculations, and identified fewer safety outcome events at 30 days. We believe this in part contributed to modelling issues when attempting to evaluate the safety outcome at 30 days. However, more than 700 patients had a myocardial infarction or cardiac death at 1 year, and the rates of all secondary outcome measures were lower following implementation of the early rule-out pathway. Third, the standard care arm of our trial used a serial testing strategy based on the time of onset of symptoms, rather than a fixed time point 3-6 hours from presentation which is more commonly used in other countries. Despite this limitation, 50% of patients were discharged directly from the Emergency Department in our standard care arm. Whilst there are differences in the inclusion criteria between trials, the proportion of patients discharged in our standard care arm was already higher than in either arm of the RAPID-TnT trial, which compared a 0/3 hour pathway (32% discharged) with a 0/1 hour pathway (45% discharged).¹⁶ Despite the high proportion of patients discharged in our standard care arm we increased the proportion discharged from 50% to 71% when implementing our early rule-out pathway. Fourth, we note that our early rule-out pathway does not recommend early serial testing in those with elevated cardiac troponin concentrations at presentation. In our previous trial,¹⁷ we observed that 2.7% of patients with suspected acute coronary syndrome have evidence of chronic myocardial injury.⁴¹ It is possible the effectiveness of our pathway could be further improved if these patients were identified in the Emergency Department. However,

patients with chronic myocardial injury are complex with significant cardiac and non-cardiac comorbidities and may benefit from further evaluation prior to discharge. Additional research to needed to evaluate the effectiveness of approaches to improve the rule-in of myocardial infarction.^{12,42} Finally, our pathway has been validated for use with two troponin I assays and a troponin T assay without modification,^{19,20,43,44} and whilst it is likely to perform similarly for other high-sensitivity assays, further research is required to confirm this.

In conclusion, implementation of an early rule-out pathway for myocardial infarction substantially reduced length of stay and increased the proportion of patients avoiding hospital admission with no increase in adverse cardiac events. Adoption of this approach would have major benefits for both patients and healthcare providers.



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Disclosures

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The HiSTORIC Investigators contributed to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work. They were involved in drafting the

manuscript and revising it, and have given final approval of the version to be published. The study sponsor had no role in the study design, collection of data, analysis and interpretation of data, writing of this report or decision to submit for publication. The corresponding author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

Supplemental Materials

List of investigators

Expanded methods

Tables I-IV and Figures I-II



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Table 1. Characteristics of the Trial Participants

	All	Standard care	Early rule-out
No. of participants	31,492	14,700	16,792
Age (years)	59±17	59±17	58±17
Women	14,252 (45)	6,575 (45)	7,677 (46)
Presenting complaint			
Chest pain	26,590 (84)	12,566 (85)	14,024 (84)
Dyspnoea	957 (3)	420 (3)	537 (3)
Palpitation	928 (3)	432 (3)	496 (3)
Syncope	1,701 (5)	699 (5)	1,002 (6)
Other	1,316 (4)	583 (4)	733 (4)
Past medical history			
Myocardial infarction	2,573 (8)	1,371 (9)	1,202 (7)
Ischaemic heart disease	7,346 (23)	3,834 (26)	3,512 (21)
Cerebrovascular disease	1,684 (5)	849 (6)	835 (5)
Diabetes mellitus	1,912 (6)	1,002 (7)	910 (5)
Previous revascularization			
PCI	2,831 (9)	1,534 (10)	1,297 (8)
CABG	452 (1)	240 (2)	212 (1)
Medications at presentation			
Aspirin	8,023 (25)	4,114 (28)	3,909 (23)
Dual anti-platelet therapy*	1,269 (4)	738 (5)	531 (3)
Statin	12,165 (39)	6,035 (41)	6,130 (37)
ACE inhibitor or ARB	9,769 (31)	4,776 (32)	4,993 (30)
Beta-blocker	8,548 (27)	4,162 (28)	4,386 (26)
Oral anti-coagulant †	2,167 (7)	1,033 (7)	1,134 (7)
Electrocardiogram ‡			
Normal	12,035 (74)	6,118 (73)	5,917 (75)
Myocardial ischemia	3,288 (20)	1,756 (21)	1,532 (20)
ST-segment elevation	193 (1)	111 (1)	82 (1)
ST-segment depression	252 (2)	146 (2)	106 (1)
T-wave inversion	1,225 (8)	621 (7)	604 (8)
Other	1,711 (11)	927 (11)	784 (10)
Hematology and clinical chemistry			
Hemoglobin, g/L	137±22	137±20	137±23
eGFR, mL/min	81±22	81±23	82±22
Presentation hs-cTnI, ng/L	3 [1-6]	3 [1-6]	3 [1-6]
Peak hs-cTnI, ng/L	3 [1-7]	3 [1-7]	3 [1-7]
Serial (≥2) tests §	11,904 (38)	6,540 (44)	5,364 (32)
Time intervals			
Symptom onset to presentation ≤2 hrs	5,664 (18)	2,859 (19)	2,805 (17)
Presentation to first test, mins	66 [45-97]	66 [46-97]	65 [43-97]
First to second test, mins	351 [188-553]	455 [267-601]	229 [155-405]

Presented as No. (%), mean±SD or median [25th percentile, 75th percentile].]. Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blockers; eGFR = estimated glomerular filtration rate; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention. * Two medications from aspirin, clopidogrel, prasugrel or ticagrelor. † Includes warfarin or novel oral anti-coagulants. ‡ Proportions reported for the 16,217 (51%) participants with electrocardiographic data available. § Serial testing was defined as two or more tests within 24 hours of presentation.

Table 2. Efficacy and Safety Outcomes at 30 Days and 1 Year

	All	Standard care	Early rule-out	Adjusted Odds Ratio (95% CI)*	P-value
No. of participants	n=31,492	n=14,700	n=16,792		
Efficacy outcome					
Length of stay, hrs (primary)	8.2±4.1	10.1±4.1	6.8±4.1	0.78 (95% CI 0.73 to 0.83)	P<0.001
Discharge from the ED (secondary)	19,249 (61)	7,407 (50)	11,842 (71)	1.59 (95% CI 1.45 to 1.75)	P<0.001
Safety outcome †					
30 days (primary)	113 (0.4)	57 (0.4)	56 (0.3)	1.97 (95% CI 0.95 to 4.08)	P=0.068
1 year (secondary)	703 (2.2)	396 (2.7)	307 (1.8)	1.02 (95% CI 0.74 to 1.40)	P=0.894
Other safety outcomes at 1 year					
Myocardial infarction ‡	422 (1.3)	238 (1.6)	184 (1.1)	1.10 (95% CI 0.72 to 1.68)	P=0.646
Cardiac death	319 (1.0)	176 (1.2)	143 (0.9)	1.07 (95% CI 0.69 to 1.64)	P=0.771
Cardiovascular death	452 (1.4)	249 (1.7)	203 (1.2)	0.93 (95% CI 0.66 to 1.32)	P=0.696
All-cause death	1,720 (5.5)	852 (5.8)	868 (5.2)	0.92 (95% CI 0.75 to 1.12)	P=0.385
Unplanned revascularisation §	222 (0.7)	119 (0.8)	103 (0.6)	0.60 (95% CI 0.35 to 1.03)	P=0.065
Any hospital reattendance	12,306 (39.1)	5,770 (39.3)	6,536 (38.9)	0.93 (95% CI 0.84 to 1.02)	P=0.112

Presented as geometric mean ± standard deviation or No. (%). Abbreviations: CI = confidence interval, ED = Emergency Department

* Outcomes following implementation of the early rule-out pathway are compared to those during standard care for all measures. For length of stay this is an adjusted ratio of the geometric mean rather than an odds ratio.

† Type 1, type 4b or type 4c myocardial infarction or cardiac death following discharge.

‡ Type 1, type 4b or type 4c myocardial infarction

§ Unplanned revascularisation was defined as urgent or emergency percutaneous coronary intervention or coronary artery bypass grafting from discharge to 1 year

Figure Legends

Figure 1. Schematic diagram of the HiSTORIC trial design and the early-rule out pathway

a) A high-sensitivity cardiac troponin I assay with sex-specific 99th centile thresholds was used to guide care and rule-in myocardial infarction during all phases of the trial. During a validation phase of at least 6 months, cardiac troponin testing was performed at presentation and was repeated 6 or 12 hours after the onset of symptoms if indicated. Myocardial infarction was ruled out where high-sensitivity cardiac troponin concentrations were less than the 99th centile at presentation if symptom onset was >6 hours from presentation, or following serial testing 6-12 hours from symptom onset in those presenting earlier (standard care). Sites were paired based on the expected number of patients and randomized to implement the early rule-out pathway (intervention) in one of three steps during a 6 month randomization phase. Finally, all sites completed an implementation phase of at least 6 months that was calendar matched to the validation phase where patient care was guided by the early rule-out pathway.

b) The early rule-out pathway rules out myocardial infarction at presentation in patients with cardiac troponin concentrations below a risk stratification threshold of 5 ng/L, unless they presented within 2 hours of symptom onset where testing is repeated 3 hours from presentation. Patients with cardiac troponin concentrations ≥ 5 ng/L at presentation are retested in the Emergency Department 3 hours after presentation, and myocardial infarction is ruled out if concentrations are unchanged (delta <3 ng/L) and remain below the 99th centile diagnostic threshold.

Figure 2. The HiSTORIC trial CONSORT diagram**Figure 3. Length of stay before and after implementation of the early rule-out pathway**

Shown is a density plot of the length of stay in patients evaluated before (blue) and after (red) implementation of the early rule-out pathway.

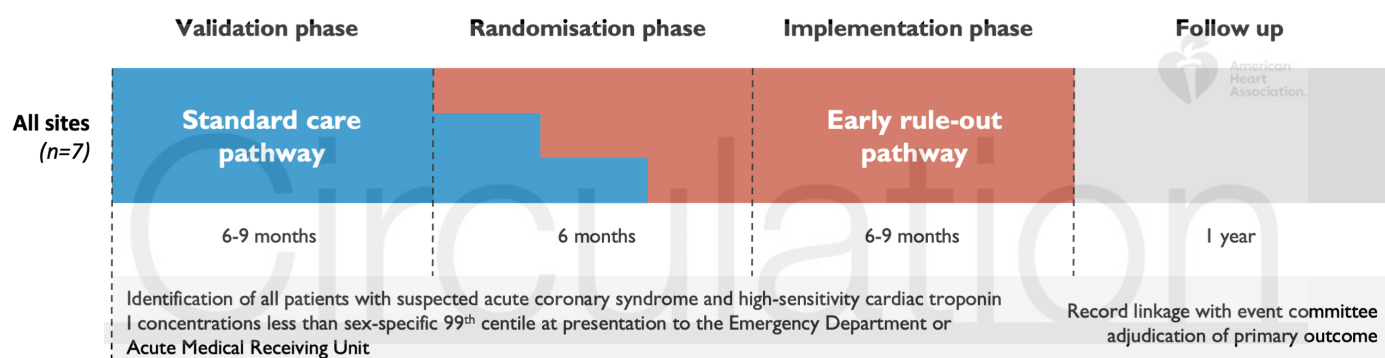
Figure 4. Myocardial infarction or cardiac death following discharge before and after implementation of the early rule-out pathway

Shown are cumulative incidence time-to-event curves for the primary safety outcome of myocardial infarction or cardiac death for patients evaluated before (blue line) and after (red line) implementation of the early rule-out pathway.



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A



B

